REMARKS

Reconsideration and allowance are respectfully requested.

Claims 1, 3-7, 9, 11-14 and 18-39 are pending. Claim 1 is amended by incorporating a limitation of claim 10 (i.e., specifying "said first agent is selected from the group consisting of avidin, streptavidin, their polymeric derivatives and their derivatives with polyethylene glycol"). Claim 14 is amended by adding "or by injection" and "in the tumor bed and surrounding tissue" to further limit "administering . . . via a locoregional route" in the independent claims. Such specificity is supported by page 6, lines 26-30, of the specification and are intended to cover a further embodiment of the invention. This latter embodiment is detailed in the enclosed recent scientific publications by the same inventors of the application in re. Claim 18 is amended by incorporating a limitation of claim 21 (i.e., specifying "said first agent is selected from the group consisting of avidin, streptavidin, their polymeric derivatives and their derivatives with polyethylene glycol"). Similarly, claim 23 is amended by adding proteins listed in claim 25 (i.e., "a protein selected from the group consisting of avidin, streptavidin, a polymeric derivative of avidin, a polymeric derivative of streptavidin, a derivative of avidin with polyethylene glycol and a derivative of streptavidin with polyethylene glycol"). New claims 30-39 are directed to an embodiment of the elected invention in which "a protein selected from the group consisting of avidin, streptavidin, a polymeric derivative of avidin, a polymeric derivative of streptavidin, a derivative of avidin with polyethylene glycol and a derivative of streptavidin with polyethylene glycol" and "a biotinylated anticancer agent" are administered. Other claims are amended to conform to their dependencies. Therefore, the amendments are fully supported by the original disclosure and no new matter is added by their entry.

35 U.S.C. 103 – Nonobviousness

A claimed invention is unpatentable if the differences between it and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art. *In re Kahn*, 78 USPQ2d 1329, 1334 (Fed. Cir. 2006) citing *Graham v. John Deere*, 148 USPQ 459 (1966). The

Graham analysis needs to be made explicitly. *KSR v. Teleflex*, 82 USPQ2d 1385, 1396 (2007). It requires findings of fact and a rational basis for combining the prior art disclosures to produce the claimed invention. See id. ("Often, it will be necessary for a court to look to interrelated teachings of multiple patents . . . and the background knowledge possessed by a person having ordinary skill in the art, all in order to determine whether there was an apparent reason to combine the known elements in the fashion claimed by the patent at issue"). The use of hindsight reasoning is impermissible. See id. at 1397 ("A factfinder should be aware, of course, of the distortion caused by hindsight bias and must be cautious of arguments reliant upon ex post reasoning"). Thus, a prima facie case under Section 103(a) requires "some rationale, articulation, or reasoned basis to explain why the conclusion of obviousness is correct." *Kahn* at 1335; see *KSR* at 1396. An inquiry is required as to "whether the improvement is more than the predictable use of prior art elements according to their established functions." Id. at 1396. But a claim that is directed to a combination of prior art elements "is not proved obvious merely by demonstrating that each of its elements was, independently, known in the prior art." Id. Finally, a determination of prima facie obviousness requires a reasonable expectation of success. See *In re Rinehart*, 189 USPQ 143, 148 (C.C.P.A. 1976).

Claims 1, 3-13 and 18-29 were rejected under Section 103(a) as allegedly unpatentable over Goldenberg (US 2001/0006618) in view of Cokgor et al. (J. Clin. Oncol. 18:3862-3872, 2000). Applicants traverse.

Example 3 of Goldenberg, which is the only example referring to tumor therapy, refers to a method that is different from the method of Applicants' claimed invention. Goldenberg describes a woman with ovarian cancer having extensive abdominal spread who is treated as follows:

1) Injection prior to surgery with a biotinylated preparation of RS7-3G11 monoclonal antibody (3 mg) i.v.

2) Three days later, a chase dose of avidin (10 mg) is given i.v. in two divided doses 60 minutes apart.

3) Twenty-four hours later, a 1.5 mg dose of biotinylated RS7-3G11 conjugated with DTPA-indium (stable) is injected i.v.

4) The next day, the patient undergoes a resection of all visible and palpable tumors in her abdominal cavity, followed by intraoperative irradiation of the exposed cavity with monochromatic X-rays of 40 keV to destroy micrometastatic cancer spread.

According to Applicants' present invention and the present set of claims, avidin is directly administered during the intraoperative locoregional phase, since it is endowed with a certain amount of tumor tropism and therefore concentrates in the therapeutic target sites, followed by systemic administration of radiolabelled biotin or biotin used as a vehicle for anticancer agents, such as, for example, chemotherapeutic agents or toxins or anticancer cells (see page 7-8 of Applicants' specification). Goldenberg does not administer avidin during surgery followed by an anticancer agent with affinity for avidin. Nothing was administered intraoperatively via a locoregional route to the patient. There was also no reason to reverse Goldenberg's order of administering avidin and biotinylated antibody.

Further data regarding the claimed method are presented by Giovanni Paganelli, an inventor of the present application in the article "IART®: Intraoperative avidination for radionuclide treatment. A new way of partial breast irradiation" *Breast* (2007), page 18, left column, fifth paragraph, which was made of record in the last IDS. Therein it was reported that the new procedure of the claimed invention, known as Intraoperative Avidination for Radionuclide Therapy (IARTs) consists of two steps: (a) "avidination" of the anatomical area of the tumor with native avidin, directly injected during surgery into and around the tumor bed and (b) targeting the anatomical area of the tumor by intravenous (i.v.) injection of radiolabelled biotin (^{90}Y), one day later.

Therefore, the first composition of Applicants' invention is different from the first composition of Goldenberg, since the former does not contain a monoclonal antibody and the former's affinity for the tumor is provided only by avidin.

Hence, Applicants' claimed method has the advantage that, following these simplified procedures, many tumors that are not targeted by their expression of specific antigens could still be treated with the reagents avidin and biotin (see page 8 of the specification). This feature of Applicants' invention is an advantage over Goldenberg's method since it allows the treatment of a broader range of tumors, namely those tumors

that do not present specific antigens. Another advantage over Goldenberg is that avidin is a much simpler, cheaper reagent than a monoclonal antibody specific for the tumor to be treated. It is immediately apparent the economic advantage of the therapeutical method according to the claimed invention, especially for the Public Health Service.

Therefore, even administering the first composition of Goldenberg locally as taught by Cokgor and the second composition parenterally as taught by Goldenberg, one of ordinary skill in the art would not have arrived at Applicants' claimed method and would not have resulted in the advantages provided by their invention as discussed herein and in the last reply.

Goldenberg does not teach or suggest that avidin could be the agent with tumor tropism, which is necessary for performing the first step of tumor targeting. This feature of avidin is also required to administer it primarily to localize in the tumor (i.e., "capable of concentrating locally on the tumor cell or in the vicinity of it"). Clearly, Goldenberg teaches that tumor targeting is achieved with a tumor-specific monoclonal antibody and that the antibody could be conjugated with avidin or biotin without difference. Thus, Goldenberg does not make one of ordinary skill in the art aware that avidin could be used as tumor targeting agent (cf. paragraph [0036] of US 2001/0006618).

To this end, both Goldenberg's and Cogkor's disclosures are concurrent: a tumor specific monoclonal antibody is the only agent with tumor tropism taught by them.

Regarding the Examiner's comments on the role of the blood-brain barrier, Applicants' claimed method is applicable not only to brain tumors but also to various breast, pancreas, lung, pleural, peritoneal, cervico-facial and bladder tumors. For this reason, we filed with the last reply two articles of Giovanni Paganelli, an inventor of the present application (i.e., "IARTs: Intraoperative avidination for radionuclide treatment. A new way of partial breast irradiation" *Breast* (2007) and "Intraoperative avidination for radionuclide therapy: A prospective new development to accelerate radiotherapy in breast cancer" *Clin Cancer Res* (2007)), which present the results obtained with the presently claimed method in treating breast tumors and demonstrate that IARTs is a simple and feasible procedure that may improve breast cancer patients' postsurgical management by shortening radiotherapy duration.

The results of this study suggest that the IARTs procedure succeeds in creating a new receptor on the tumor that is able to concentrate labeled DOTA-biotin i.v. injected one day after breast cancer conserving surgery (CS) (Paganelli et al., *Breast* (2007), page 23, fourth paragraph).

Applicants' claimed method provides the following advantages (see Paganelli et al., *Breast* (2007), page 24, left column, fifth paragraph; right column, first and third paragraphs):

- Multifocal tumors, tumor location and tumor size are not limiting factors. Avidin is injected all around the tumor bed, without limitations in terms of depth, volume and margins during surgery.
- No dedicated linear accelerator, nor other devices or technological equipment is required. IARTs can be applied worldwide in all centers where breast surgery is performed and a nuclear medicine unit is present. ^{90}Y-radiolabelled biotin can be prepared in a central radiopharmacy and delivered within a few hours to a facility requiring the doses of radiopharmaceuticals for patients who were operated on the previous day. Logistically, this should facilitate the widespread use of CS and accelerated radiotherapy especially for patients presenting logistical barriers to travelling.
- The absorbed doses to the most involved normal organs (urinary bladder, kidneys) were far from the threshold doses of tissue side effects reported in the literature.

These advantages are not limited to the therapy of breast cancer but are provided by the present method when applied to all solid tumors.

Claims 1, 3-14 and 18-29 were rejected under Section 103(a) as allegedly unpatentable over Goldenberg (US 2001/0006618) in view of Cokgor et al. (J. Clin. Oncol. 18:3862-3872, 2000) and MacPhee et al. (US 6,054,122). Applicants traverse.

In view of the present amendments to the claims and the data provided in the two aforementioned articles, Applicants rely on the arguments presented herein and in our previous reply and submit that the claimed methods are not obvious over Goldenberg in

view of Cokgor and MacPhee. The deficiencies of Goldenberg in view of Cokgor noted above are not remedied by the addition of MacPhee.

Moreover, it is submitted that MacPhee is not relevant to the claimed methods because the newly cited document solves the problem of treating wounded tissue. One of ordinary skill in the art would not have received any guidance from MacPhee and would not have looked to its disclosure when confronted with an invention related to the technical field of tumors and their treatment. MacPhee discloses spray application for external wounds but not for internal application, such as during a surgical procedure (column 25, lines 38-44). In Applicants' claimed method, the agent that can be administered by spray is the first agent which is administered intraoperatively via a locoregional route.

Further, there is no reasonable expectation of success that Goldenberg's cancer treatment agent used in Cokgor's administration method could be practiced intraoperatively with spray administration. MacPhee provides no evidence of such reasonable expectation of success, which is required for prima facie obviousness, and no other evidence or reasoning is provided in the Office Action.

Withdrawal of the Section 103 rejections is requested because the claims would not have been obvious to one of ordinary skill in the art when this invention was made.

Having fully responded to the pending Office Action, Applicants submit that the claims are in condition for allowance and earnestly solicit an early Notice to that effect. The Examiner is invited to contact the undersigned if additional information is required.

Respectfully submitted,

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